Surgical Endoscopy (2021) 35:2750–2758
https://doi.org/10.1007/s00464-020-07706-1

Benefits of linked color imaging for recognition of early differentiated-type gastric cancer: in comparison with indigo carmine contrast method and blue laser imaging

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Received: 28 February 2020 / Accepted: 9 June 2020 / Published online: 16 June 2020

Abstract

Background and aim Linked color imaging (LCI) is a novel endoscopy system, which enhances slight differences in mucosal color. However, whether LCI is more useful than other kinds of image-enhanced endoscopy (IEE) in recognizing early gastric cancer remains unclear. This study aimed to evaluate LCI efficacy compared with the indigo carmine contrast method (IC), and blue laser imaging-bright (BLI-brt) in early differentiated-type gastric cancer recognition.

Methods We retrospectively analyzed early differentiated-type gastric cancer, which were examined by all four imaging techniques (white light imaging, IC, LCI, BLI-brt) at Asahi University Hospital from June 2014 to November 2018. Both subjective evaluation (using ranking score: RS) and objective evaluation (using color difference score: CDS) were adopted to quantify early differentiated-type gastric cancer recognition.

Results During this period, 87 lesions were enrolled in this study. Both RS and CDS of LCI were significantly higher ($p < 0.01$) than those of IC and BLI-brt. Both RS and CDS of BLI-brt had no significant difference compared with those of IC. Subgroup analysis revealed that LCI was especially useful in post-*Helicobacter pylori* eradication patients and flat or depressed lesions compared with IC and BLI-brt.

Conclusions LCI appears to be more beneficial for the recognition of early differentiated-type gastric cancer in endoscopic screenings than IC and BLI-brt from the middle to distant view.

Keywords Image-enhanced endoscopy · Linked color imaging · Blue laser imaging · Indigo carmine contrast

Helicobacter pylori (HP) is present in many people and is closely associated with gastric cancer worldwide [1, 2]. Although the importance of HP eradication therapy has been recognized worldwide, mortality due to gastric cancer is still in high ratio. Even when eradication therapy is successful, gastric cancer is still diagnosed in 0.2% of the population annually [3]. Gastric cancer recognition in post-eradication gastric mucosa is difficult because (a) some gastric cancers lose their elevation after eradication and (b) normal columnar epithelium or low-grade atypia frequently spreads onto the neoplasm [4, 5]. Hence, image-enhanced endoscopy (IEE) techniques will play more important roles in gastric cancer detection.

In Japan, the indigo carmine contrast method (IC), spraying indigo carmine to the whole gastric mucosa, was widely used as chromoendoscopy to detect early gastric cancer [6]. However, few clinical studies have been conducted regarding indigo carmine's effectiveness in detecting gastric cancer. Alternatively, the usefulness of new IEE techniques in detecting and diagnosing early gastric cancer has been reported, such as flexible spectral imaging color enhancement (FICE) or narrow-band imaging (NBI) [7, 8]. Unfortunately, FICE cannot show clear high contrast images of the mucosal surface, and NBI cannot gain enough light intensity from a distant view. Recently, a new endoscopic system called LASEREO (FUJIFILM Co., Tokyo, Japan) was developed. LASEREO generates observation lighting

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from the combination of fluorescence and two kinds of laser: a 450 nm wavelength for white light imaging (WLI) and a 410 nm wavelength for blue laser imaging (BLI). BLI is one of the IEE method that enables narrow-band light observation, which is useful in diagnosing gastric cancer with magnification based on the light-absorption characteristics of hemoglobin. Moreover, BLI-bright (BLI-brt) is a brighter BLI mode that is useful for endoscopic observation from middle to distant view [9]. Nonetheless, when observing the gastric mucosa for screening, the light intensity of BLI-brt is still insufficient. That being the case, linked color imaging (LCI) had developed as a new IEE system. LCI enhances the slight difference in mucosal color, and the lighting in LCI mode has a high ratio of short wavelength light intensity, which emphasizes hemoglobin-related information. The reddish color is a key color for the diagnosis of gastric diseases. Signal processing of LCI emphasizes the contrast of the reddish color, while colors far from red are not changed. Recently, some studies reported that LCI was significantly useful for the diagnosis of active HP infection or gastric intestinal metaplasia [10–12]. Furthermore, a few previous studies indicated LCI's effectiveness in gastric cancer recognition compared with conventional WLI [13–15]. However, it remains to be clarified whether LCI is more beneficial for recognizing gastric cancer when compared with other kinds of IEE, including chromoendoscopy.

The present study aimed to evaluate the usefulness of LCI compared with IC and BLI-brt for the recognition of early differentiated-type gastric cancer. Both subjective and objective evaluation methods were adopted to quantify early differentiated-type gastric cancer recognition.

Materials and methods

Study design

This study was a retrospective, single-center study conducted at Asahi University Hospital. Therefore, opt-out method was adopted and written consent was not required. This study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) registration number UMIN 000033646. The study was approved by the ethics committee of the Asahi University Hospital (No. 2018-04-01) and was conducted in accordance with the Helsinki Declaration of the World Medical Association and the Ethical Guidelines for Medical and Health Research Involving Human Subjects established by the Ministry of Health, Labour and Welfare, JAPAN.

Patients

We retrospectively analyzed early differentiated-type gastric cancer, which were examined by all four imaging techniques (WLI, IC, LCI, and BLI-brt) before endoscopic submucosal dissection (ESD) at Asahi University Hospital from June 2014 to November 2018. We excluded patients who were examined by endoscopy in which the LCI mode was not mounted, who were not examined by all four imaging techniques, and who were diagnosed with tubular adenoma or signet ring cell carcinoma histopathologically. Gastric adenoma was excluded because there are many institutions that have different clinical treatment plans for gastric cancer and gastric adenoma clinically. Additionally, signet ring cell carcinoma was excluded because the color tone of undifferentiated-type cancer is different from the differentiated type; however, the number of undifferentiated-type adenocarcinomas recruited in this period was too small. Further, undifferentiated-type adenocarcinoma is less frequently indicated for ESD; hence, we considered it is not appropriate to evaluate both differentiated-type and undifferentiated-type adenocarcinomas in the same data set (Fig. 1).

Lesions

We evaluated one of each image (LCI, IC, BLI-brt, and WLI) taken from the same middle to distant point of view. The presence of HP infection was investigated before ESD based on more than two different examinations: a histological examination, serum antibody test (baseline level: 0–10.0U/ml), stool antigen test (positive or negative), and/or ^{13}C-urea breath test (baseline level: 0–2.4‰).

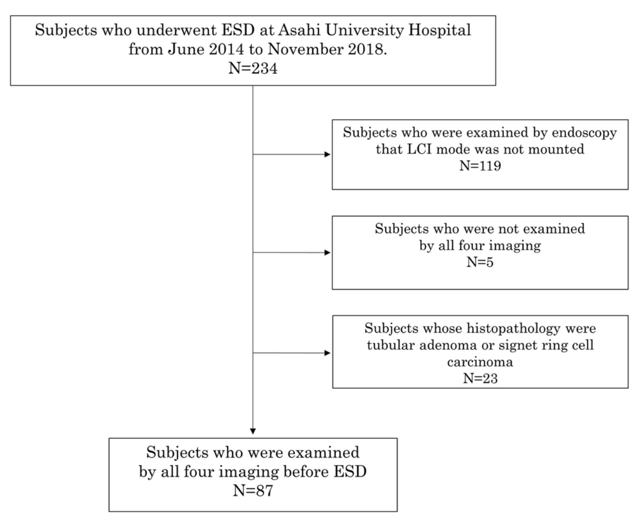


Fig. 1 Flowchart of the patients who are recruited in this study

Endoscopy system

All examinations were carried out with the LASEREO system (LL-7000/VP-7000 or LL-4450/VP-4450) and upper gastrointestinal endoscope (EG-L600ZW7 or EG-L590ZW) (FUJIFILM Co., Tokyo, Japan). These endoscopic systems have four modes: WLI, LCI, BLI, and BLI-brt. Each mode can be changed easily by pushing the button beside the operating portion. The color and structural emphasis of the LCI and BLI-brt were set to C1 and B5, respectively.

Subjective evaluation

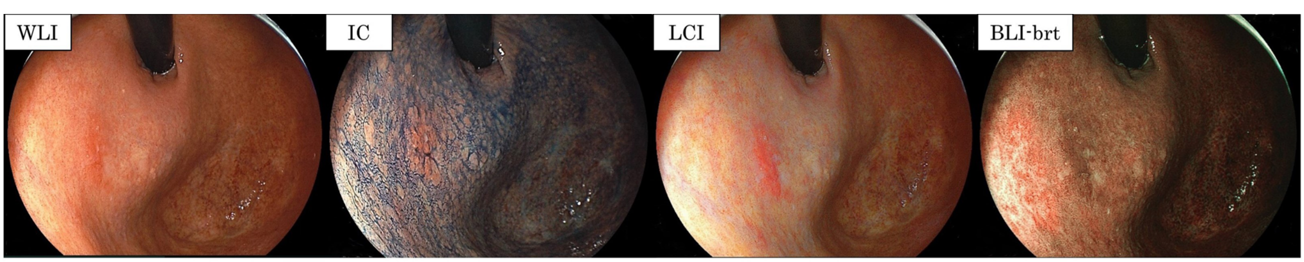
Subjective evaluation was performed using the point ranking method to analyze early differentiated-type gastric cancer detectability. Each lesion was assigned a ranking score (RS) from 3 to 0. RS 3 means excellent visibility, easy to find the lesion; RS 2 means good visibility, relatively easy to find the lesion; RS 1 means fair visibility, can barely find the lesion; and RS 0 means poor visibility, difficult to find the lesion. We displayed independently one of each non-magnified image examined with LCI, IC, BLI-brt, and WLI on the computer screen. After randomization to prevent comparison of the same lesion taken by different modes, three endoscopists evaluated each image. The professions of the three endoscopists are (A) a board-certified gastroenterologist trainer, (B) a board-certified gastroenterologist, and (C) a senior resident. They evaluated the images in separate rooms without consulting any other endoscopists (Fig. 2).

Objective evaluation

Objective evaluation was performed with the $L^*a^*b^*$ color space-based color difference scores (CDS) between inside and outside of the lesion. The $L^*a^*b^*$ color system was defined by CIE (commission internationale de l'éclairage, Vienna, Austria) in 1976 [16]. Since then, the $L^*a^*b^*$ color system has been used most frequently to evaluate color differences all over the world. In the $L^*a^*b^*$ color system, color is depicted by three dimensions: the a^*–b^* plane expresses *Hue* and *Saturation,* the L^*-axis expresses *Brightness*. Additionally, the a^*-axis depicts the tone of red to green color. On the other hand, the b^*-axis depicts the tone of yellow to blue color. We used this system to evaluate the CDS between inside and outside of the lesion. The region of interest (ROI) was selected as 40×40 pixels. On the inside of the lesion, the ROI was selected using two points that were located in the 3 o'clock and 9 o'clock directions. On the outside of the lesion, the ROI was also selected using two points that were located in the 3 o'clock and 9 o'clock directions just out of the lesion (Fig. 3). The 6 o'clock direction of some images was not suitable to evaluate the color difference due to the halation. The 12 o'clock direction was also not suitable in some cases to evaluate the color difference because the images were not bright enough. Hence, we chose the ROI from the 3 o'clock and 9 o'clock directions. The ROI was deployed to almost the same place per patient. CDS was calculated using the CIE76 formula [17]: $\Delta = [(\Delta^*)^2 + (\Delta^*)^2 + (\Delta^*)^2]^{1/2}$. The average color value was calculated using Adobe Photoshop Elements (Adobe Inc, USA).

Statistical analysis

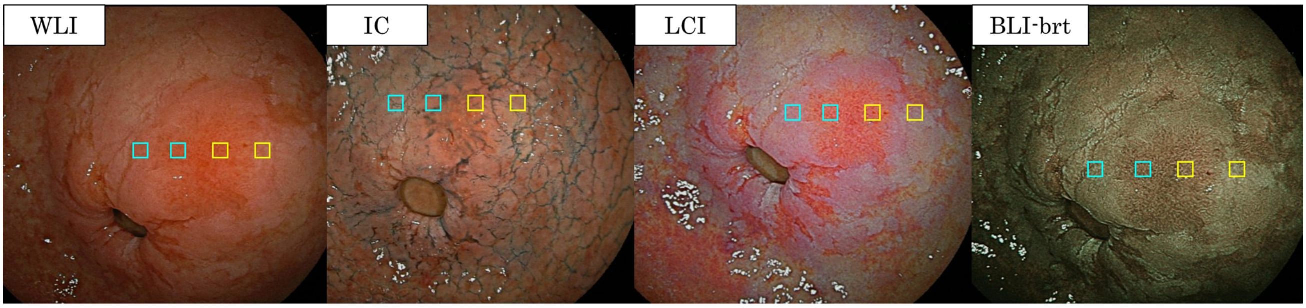
A mixed effect model was used to examine the relationships between methods, i.e., methodological differences (objective, subjective) and the difference in color as a fixed effect, and inter-subject difference as a random effect. All images are reviewed by all three reviewers. However, the reviewer variation was very small, we neglected the variation in the



	WLI	IC	LCI	BLI-brt
A	1	2	3	1
B	1	3	3	2
C	2	3	3	2

Excellent visibility	3
Good visibility	2
Fair visibility	1
Poor visibility	0

Fig. 2 An example of subjective evaluation which uses ranking score



	Area	WLI	IC	LCI	BLI-brt
L*	Inside (average)	140.29	143.28	164.46	101.23
	Outside (average)	142.89	163.24	170.02	138.97
a*	Inside (average)	176.74	158.99	176.80	133.13
	Outside (average)	166.70	145.34	132.98	128.41
b*	Inside (average)	175.18	156.98	157.38	147.35
	Outside (average)	161.60	148.77	132.93	147.50
CDS	ΔE*	16.92	17.73	34.20	23.04

Fig. 3 An example of objective evaluation which uses color difference score

model. The mixed effect model is useful in the repeated measures design which frequently observes certain items in the time-course study. This model is often preferable to traditional approaches such as repeated measures analysis of variance. The structure of the current mixed effect model includes the general effect, the fixed effect (subjective or objective), the random effect (variation between subjects), the interaction where color difference is depending on methods (subjective or objective), and type III error.

We used Tukey's multiple comparison test to compare the RS or CDS across all four images. All statistical analyses were two-tailed, and $p < 0.05$ was regarded as statistically significant. All statistical analyses were performed using JMP version 13.2 (SAS Institute Inc, Cary, NC, USA).

Results

Of 234 lesions assessed for trial eligibility, 147 were excluded; of these, 119 were examined by endoscopy that LCI mode was not mounted, 5 were not examined by all four imaging, and 23 were tubular adenoma or signet ring cell carcinoma histopathologically. The remaining 87 lesions met inclusion criteria (Fig. 1). Macroscopic classification was as follows: type 0-IIa: 28 cases, type 0-IIb or IIc: 57 cases, and type 0-I: 2 cases. The location of the lesion was as follows: antrum: 25 cases, angle: 18 cases, lower body: 23 cases, middle body: 5 cases, upper body: 9 cases, fornix: 2 cases, and cardia: 5 cases. The histopathology results were as follows: tub1: 78 cases and tub2: 9 cases. The background gastric mucosa was as follows: HP current infection: 46 cases, post-eradication: 39 cases, and HP uninfected: 2 cases (Table 1).

The analysis of variance table for the mixed effects model is shown in Table 2. The results of the mixed effect model showed significantly high effects in methods, color difference, and their interaction ($p < 0.01$). The random effect also showed significant differences ($p < 0.01$). The interaction plot revealed that both assessments of RS and CDS showed a bell shape, with a peak at LCI (Fig. 4). The correlation coefficients between RS and CDS were 0.38 for WLI, 0.61 for IC, 0.43 for LCI, and 0.43 for BLI-brt. WLI showed a weak positive correlation, and other three modes showed positive correlations between the subjective and objective evaluations.

Total analysis

The overall average RS (Fig. 5A) of LCI was significantly higher than that of IC and BLI-brt (2.51 ± 0.47 vs. 2.23 ± 0.65 and 2.02 ± 0.53), respectively ($p < 0.01$) (Tukey's multiple comparison test). There were no significant differences between the overall average RS of IC and BLI-brt ($p = 0.054$).

The overall average CDS (Fig. 5B) of LCI was significantly higher than that of IC and BLI-brt (25.57 ± 5.93

Table 1 Baseline characteristics of patients recruited for this study

Age (years), median (IQR)	74 (54–92)
Gender, *n* (%)	
Male	55
Female	32
HP infection	
Current infection	46
Post eradication	39
Uninfected	2
Mucosal atrophy	
Closed type	9
Open type	78
Morphological type	
0-IIa	28
0-IIb	15
0-IIc	42
0-I	2
Location	
Antrum	25
Angle	18
Lower gastric body	23
Middle gastric body	5
Upper gastric body	9
Fornix	2
Cardia	5
Histopathology	
tub1	78
tub2	9
Depth	
M	77
SM1	3
SM2	7

vs. 19.59 ± 5.94 and 20.25 ± 4.99), respectively ($p < 0.01$). There was no significant difference between overall average CDS of IC and BLI-brt ($p = 0.852$).

Subgroup analysis based on morphologic type

Subgroup analysis based on morphologic type revealed that both average RS and average CDS of LCI for type 0-IIb or 0-IIc lesions (57 lesions) (Fig. 6A, B) were significantly higher than those of IC or BLI-brt ($p < 0.01$). There was no difference between IC and BLI-brt (RS: $p = 0.542$, CDS: $p = 0.852$).

Alternatively, regarding type 0-IIa lesions (28 lesions) (Fig. 6C), the average RS of IC as well as LCI was significantly higher than that of BLI-brt (IC to BLI-brt: $p = 0.028$, LCI to BLI-brt: $p = 0.022$). There was no significant difference between the average RS of LCI and IC ($p = 0.999$). The average CDS of LCI was significantly higher than that of BLI-brt ($p = 0.003$) (Fig. 6D). There was no significant difference between the average CDS of LCI and IC ($p = 0.084$), or IC and BLI-brt ($p = 0.626$).

Subgroup analysis based on HP infection

Subgroup analysis based on HP infection revealed that, regarding current infection cases (46 lesions), the average RS of IC as well as LCI was significantly higher than that of BLI-brt (IC to BLI-brt: $p = 0.044$, LCI to BLI-brt: $p = 0.003$) (Fig. 7A). There was no significant difference between the average RS of LCI and IC ($p = 0.804$). The average CDS of LCI was significantly higher than that of IC or BLI-brt ($p < 0.01$). There was no significant difference between IC and BLI-brt ($p = 0.999$) (Fig. 7B).

On the other hand, regarding the post-eradication cases (39 lesions), both RS and CDS of LCI were significantly higher than those of IC or BLI-brt ($p < 0.01$) (Fig. 7C, D). Furthermore, there was no significant difference between RS of IC and BLI-brt ($p = 0.898$) or between CDS of IC and BLI-brt ($p = 0.479$).

Subgroup analysis based on the brightness

Subgroup analysis of L^*-axis, which expresses brightness in the CDS, revealed that the average L^* of inside the tumor

Table 2 Analysis of variance table for the mixed effects model

SOV	df	Sum sq	Mean sq	*F*	Prob > *F*	Significance
Method	1	53,180.39	53,180.39	5622.84	< 0.01	**
Color Diff	3	3774.76	1258.25	133.04	< 0.01	**
Subjects	172	5015.38	29.16	3.08	< 0.01	**
Method × Color Diff	3	3055.93	1018.64	107.70	< 0.01	**
Error	516	4880.29	9.46			
Total	695	69,906.75				

SOV Source of Variance, *df* degree of freedom, *Sum sq*. sum of squares, *Mean sq*. mean squares, *F* F statistic, *Prob* probability

*$p < 0.05$; **$p < 0.01$

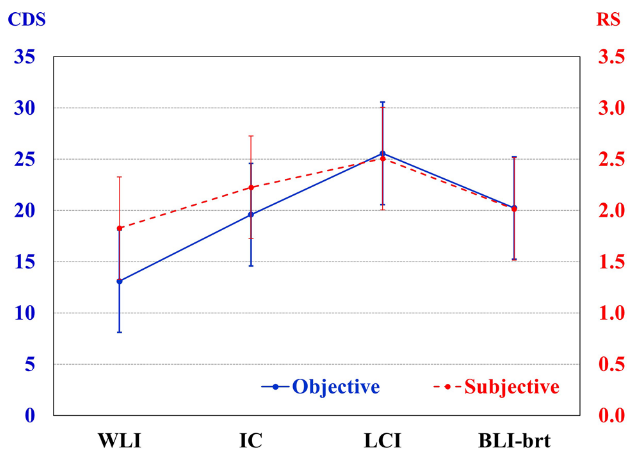


Fig. 4 The interaction plot revealed that both subjective and objective evaluations showed a bell shape, with a peak at LCI

was as follows: LCI, 55.08; IC, 47.94; BLI-brt, 39.16. The average L^* of outside the tumor was as follows: LCI, 60.43; IC, 47.74; BLI-brt, 50.73. The brightness of LCI was significantly higher than IC and BLI-brt ($p < 0.01$) regardless of inside and outside the lesion.

Discussion

This is the first study that investigates the efficacy of LCI in comparison with chromoendoscopy and BLI-brt for the recognition of early differentiated-type gastric cancer using both subjective and objective evaluations. Oftentimes, early gastric cancer is difficult to find; therefore, IEE methods such as chromoendoscopy, NBI, and BLI have been adopted for the detection of early gastric cancer. Some reports showed that BLI exhibits a similar ability as that of NBI in the detection of early upper gastrointestinal cancer [18, 19]. A few previous studies indicated the usefulness of LCI when compared with WLI for the detection of gastric cancer [13–15]. However, no clinical studies investigated the usefulness of LCI compared with IC or BLI-brt for gastric cancer recognition. IC, which has some disadvantages in screening endoscopy (i.e., taking time for splaying color, sometimes masking the tumor surface, and cost-consuming), is widely used for detecting the margins of gastric cancer [20], and it is reportedly not inferior to magnifying NBI about the delineation of gastric cancer margins [21]. However, there has been little evidence about the utility of IC in the detection of gastric cancer.

To evaluate the visibility of early differentiated-type gastric cancer, we used both subjective and objective evaluations using RS and CDS, respectively. RS was evaluated by judging the three endoscopists in our hospital, and CDS was calculated inside and outside the lesion using $L^*a^*b^*$ color space. Generally, gastric cancer is detected by the color difference and morphological change [22]. RS reflects color contrast and morphological change, and CDS evaluates only the color contrast. The correlation coefficients between RS and CDS were 0.38 to 0.61 for the averages of each mode. Given this information, RS and CDS showed positive or weak positive correlation. The interaction plot of both RS and CDS showed a bell shape with a peak at LCI.

Both subjective and objective evaluations revealed that the LCI mode was most useful for the recognition of early differentiated-type gastric cancer compared with IC and BLI-brt regardless of the morphological type or HP infection state. Furthermore, both subjective and objective evaluations indicated that there was no significant difference between BLI-brt and IC.

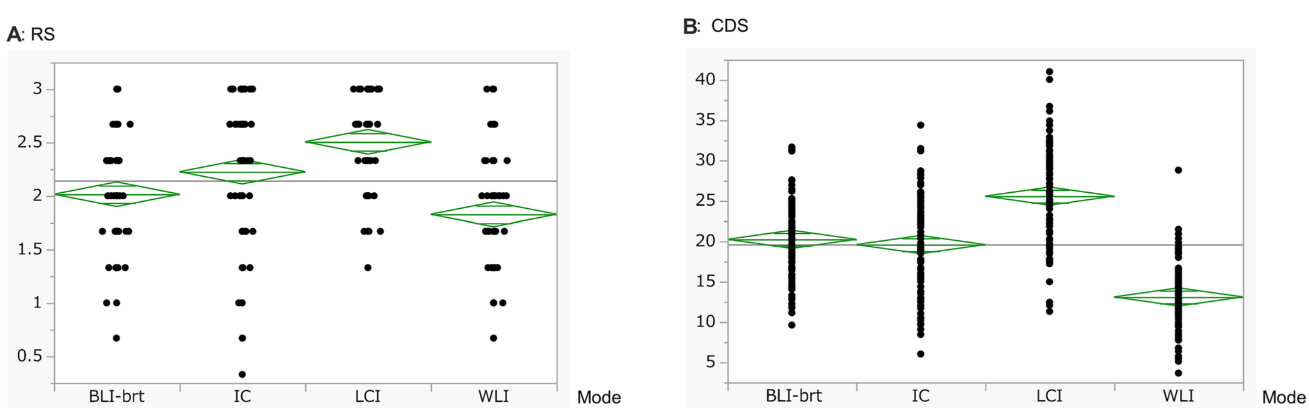


Fig. 5 The result of overall **A** average RS and **B** average CDS among four modes (Tukey's multiple comparison test). The overall average RS of LCI was significantly higher than that of IC and BLI-brt, respectively. There were no significant differences between the overall average RS of IC and BLI-brt (**A**). The overall average CDS of LCI was significantly higher than that of IC and BLI-brt, respectively. There was no significant difference between overall average CDS of IC and BLI-brt (**B**)

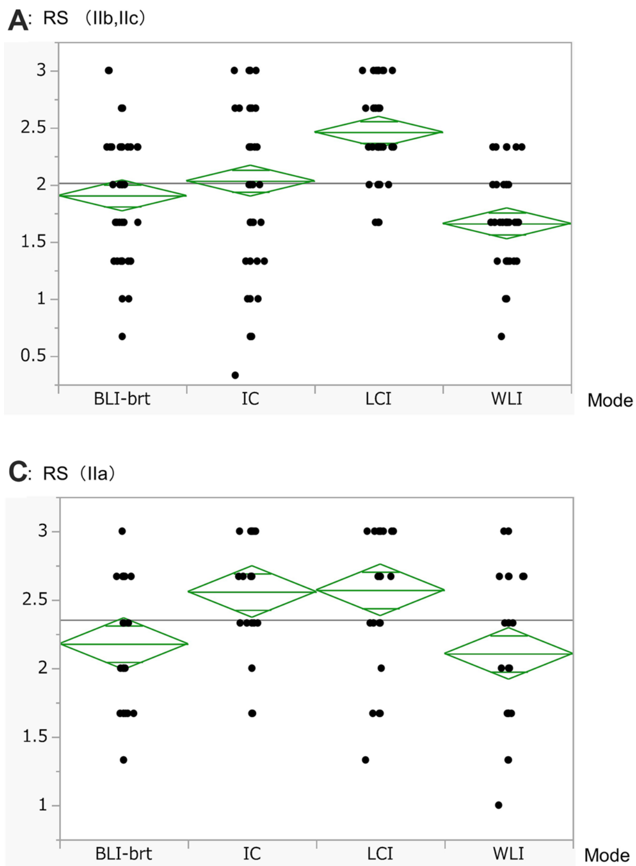


Fig. 6 Subgroup analysis of the **A** average RS about 0-IIb or IIc lesions, **B** average CDS about 0-IIb or IIc lesions, **C** average RS about 0-IIa lesions, **D** average CDS about 0-IIa lesions among four modes (Tukey's multiple comparison test)

From the viewpoint of subgroup analysis on L^*-axis, the detectability of early differentiated-type gastric cancer would be affected by the brightness of a visual field of endoscopy.

Subgroup analysis of 0-IIa lesions revealed that there were no significant differences between LCI and IC in both subjective and objective evaluations. IC would also be useful in the detection of elevated-type lesions. Conversely, subgroup analysis of 0-IIb or IIc lesions revealed that there were significant differences between LCI and IC in both subjective and objective evaluations.

Subgroup analysis of current HP-infected lesions revealed that LCI and IC got high scores without significant differences and BLI-brt ranked next in subjective evaluations. In objective evaluations of current HP-infected lesions, there were no significant differences between BLI-brt and IC. In contrast, subgroup analysis of post-eradicated lesions revealed that LCI has high visibility with significant differences compared with IC and BLI-brt in both subjective and objective evaluations.

In recent years, HP eradication therapy has become widely performed throughout the world, with an increase in the number of post-eradication patients. Some studies have reported that several gastric cancers were discovered after successful HP eradication occurred in the advanced atrophy mucosa, and they represented well-differentiated flat or depressed types, located in the middle to lower part of the stomach [23, 24]. Furthermore, according to the past report, the diagnostic reliability of IC is lower than that of WLI in after eradication cases [25]. In our study, LCI was more useful than IC or BLI-brt especially for post-eradication cases and flat or depressed lesions. As the post-HP eradication patients have been increasing, LCI would play a significant role in identifying early differentiated-type gastric cancer.

Regarding IC, our study revealed this method was useful especially for recognizing elevated-type lesions or HP current infected cases. Generally, IC could emphasize the morphologic type of the tumor, but given our study IC also exhibited the color differences present inside and outside of the lesion. It is possible that the difference of the amount of indigo carmine which accumulates into the crypt-opening would generate the contrast of color.

Regarding BLI-brt, past study showed its usefulness for detecting early gastric cancer [9]. Our study also observed significant differences in the CDS of BLI-brt compared with

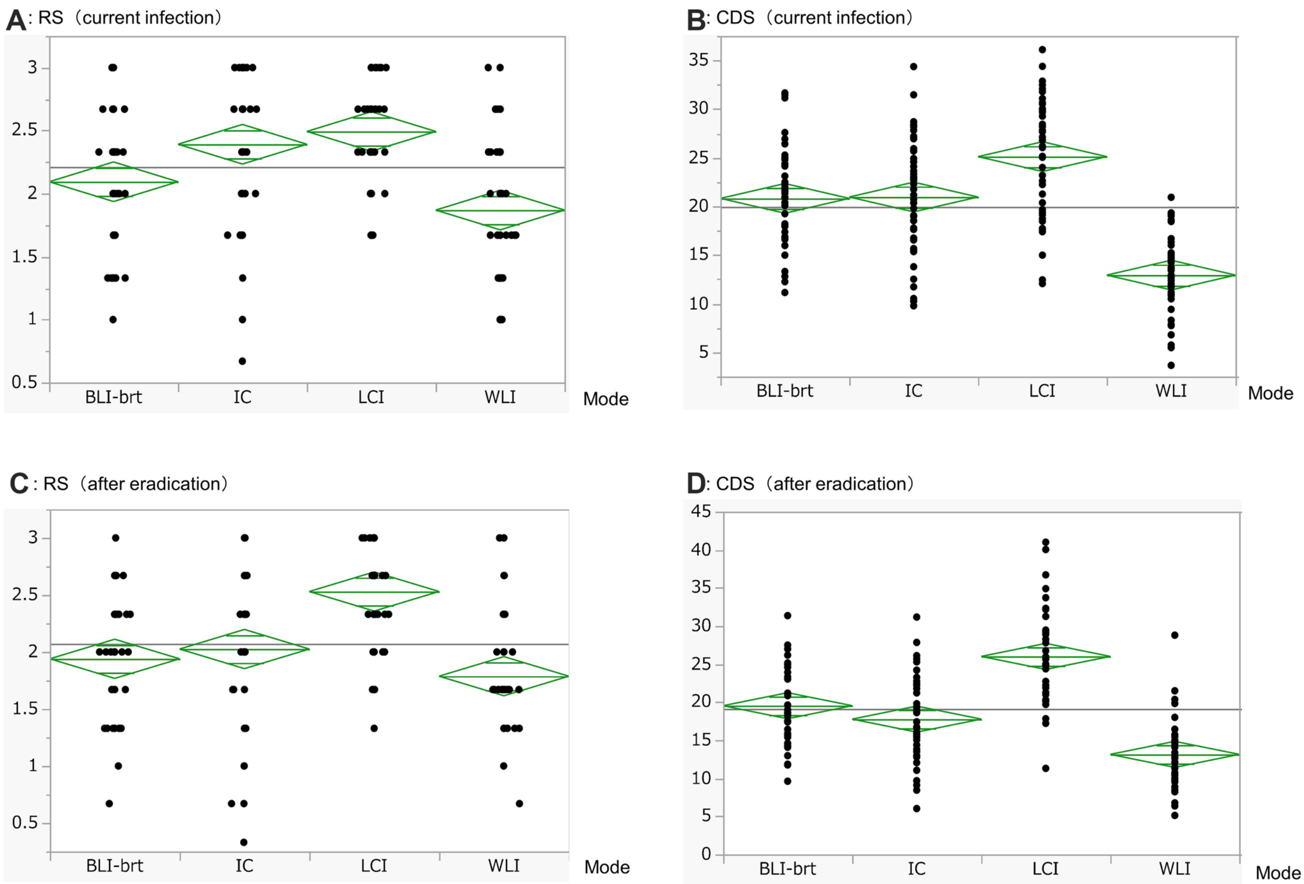


Fig. 7 Subgroup analysis of the **A** average RS about current HP-infected patients, **B** average CDS about current HP-infected patients, **C** average RS about post-eradication patients, **D** average CDS about post-eradication patients among four modes (Tukey's multiple comparison test)

WLI. The RS of BLI-brt showed the same tendency; however, the CDS and RS of BLI-brt was not superior to other kinds of IEE in this study. Subgroup analysis of the brightness showed less light intensity than LCI. Considering this result, BLI-brt shows a good contrast between a lesion's inside and outside, but from a distant point of view, some lesions would be difficult to recognize because of the low brightness.

This study had several limitations. First, it was conducted in a single center, and we collected the data retrospectively. As a result, this study cannot equally adapt to undetected lesions, and we could not evaluate the false-positive or false-negative rate by using new IEE techniques. Second, we evaluated still images instead of videos. Prospective multicenter studies are required to verify the effectiveness of LCI compared with other IEE methods for the recognition of undetected gastric cancer.

Conclusion

We retrospectively evaluated early differentiated-type gastric cancer recognition and found that LCI was more effective than IC and BLI-brt in the visibility of early differentiated-type gastric cancer, especially for post-HP eradication cases and flat or depressed types. LCI would appear to be useful in the clinical setting for recognizing an early gastric cancer from the middle to distant view.

Acknowledgements The authors wish to acknowledge Dr. S. Sugie, a professor in the Department of Diagnostic Pathology, Asahi University Hospital for the useful discussions. We also thank the anonymous reviewers for their helpful comments.

Compliance with ethical standards

Disclosures Yuji Naito received scholarship funds from EA Pharma. Co. Ltd. and collaboration research funds from Fujifilm Medical Co., Ltd., and Taiyo Kagaku Co. Ltd. and has been paid lecture fees by Mylan EPD Co., Takeda Pharma. Co. Ltd., Mochida Pharma. Co. Ltd., EA Pharma. Co. Ltd., Otsuka Pharma. Co. Ltd., Nippon Kayaku Co. Ltd., and Miyarisan Pharma. Co. Ltd. Yoshito Itoh received collaboration research fund from Takeda Pharma. Co. Ltd., Daiichi Sankyo Co., Ltd, Otsuka Pharma. Co. Ltd., Eisai Co. Ltd., and EA Pharma. Co. Ltd. and has been paid lecture fees by AstraZeneca K.K. Neither the funding agency nor any outside organization participated in the study design, and there are no competing interest. Drs. Takeshi Yasuda, Nobuaki Yagi, Tatsushi Omatsu, Yuriko Yasuda, Yuki

Nakahata, Sadanari Hayashi, Akihiro Obora, and Takao Kojima have no conflicts of interest or financial ties to disclose.

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